

# Frontonasal Malformation and Cloacal Exstrophy: A Previously Unreported Association

Nathaniel H. Robin, Julie A. Neidich, Lynn D. Bason, Linton A. Whitaker, Donna McDonald-McGinn, Jill Hunter, Howard M. Snyder III, and Elaine H. Zackai

*Division of Human Genetics and Molecular Biology (N.H.R., L.D.B., D.M.-M, E.H.Z.), Departments of Plastic and Reconstructive Surgery (L.A.W.), Radiology (J.H.), and Urology (H.M.S.), The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, and Division of Human Genetics (J.A.N.), Stanford University School of Medicine, Stanford, California*

**We report on a child with frontonasal malformation (FNM) and cloacal exstrophy, a combination of findings that have not been reported previously. In FNM and cloacal exstrophy, associated malformations are rare. FNM and cloacal exstrophy both represent abnormalities of the development of the midline field; this combination of anomalies in this patient suggests an impairment of caudal and cranial midline development during blastogenesis.** © 1996 Wiley-Liss, Inc.

**KEY WORDS:** frontonasal malformation, median cleft face, frontonasal dysplasia, midline field defect, midline development

## INTRODUCTION

Frontonasal malformation (FNM) and cloacal exstrophy are malformations involving the midline developmental field. Each is usually seen as an isolated finding in the affected individual; associated malformations are rare [Cohen et al., 1971].

Here we report on a female infant born with FNM and cloacal exstrophy, a previously unreported combination of findings in a single patient. As both malformations are anomalies of the developing midline, the occurrence of these two malformations in this patient suggests that an insult affecting the caudal and rostral midline fields occurred at approximately 4–6 weeks gestation.

## CLINICAL REPORT

The patient was a 2,850 g term (40th centile) product of a 17-year-old G1 woman, born by an uncomplicated vaginal delivery. The prenatal history was remarkable for alcohol use of undetermined quantity throughout the pregnancy. At birth (Figs. 1, 2a,b), the infant female was noted to have a prominent bilateral cleft of the lip, palate, and uvula. The nares were separated by the cleft, with a single nostril present on either side. In addition, there was cloacal exstrophy, with ambiguous genitalia and an imperforate anus, and equinovarus deformities of both feet. Radiographic exam documented a divided lumbar, sacral, and coccygeal portion of the vertebral column. In addition, during surgery to place a distal colostomy, she was found to have short gut syndrome. And later, while undergoing vaginoplasty, it was discovered that she had a duplication of her vagina, cervix, and uterus.

Now, at age 15 years, she is a healthy young girl. She is doing well in school with remedial help, and has been diagnosed with dyslexia. Despite her urogenital anomalies, she is continent of urine, although she still has the colostomy. She now has a head circumference of 54.5 cm (50th centile), a height of 140 cm (<5th centile, 50th centile for a 10-year-old), interpupillary distance of 6.7 cm (>95th centile), a broad nose with a notched nasal tip, a dextro-scoliosis, and atrophy of her right leg. A recent MRI of her lumbosacral spine detailed the vertebral malformation, with multiple associated vertebral body anomalies (Fig. 3).

## DISCUSSION

FNM, also known as frontonasal dysplasia and median cleft face syndrome, is a midline developmental field defect of the frontonasal prominence [Cohen et al., 1971]. The primary pathophysiologic event in the development of FNM is thought to be a failure of the formation of the nasal capsule, sometime around the 4th week of gestation. This failure of development allows the primitive brain vesicle to fill the space normally occupied by the nasal capsule, thus preventing closure of the anterior cranium. This, in turn, causes an arrest of

Received for publication April 30, 1995; revision received July 11, 1995.

Address reprint requests to Nathaniel H. Robin, M.D., University Hospital of Cleveland, Center for Human Genetics, Case Western Reserve University School of Medicine, Lakeside 1500, 11100 Euclid Ave., Cleveland, OH 44106.



Fig. 1. The patient at birth.

the migration of the placement of the optic vesicles, nasal placodes, and a poorly formed nasal tip [Cohen et al., 1971]. Experimental models have produced findings that have supported this theory: teratogen-induced early and excessive cell death of the midline mesenchyme of the frontonasal prominence produces the FNM phenotype in mice [Burk and Sadler, 1983].

In most cases, FNM is an isolated finding, as associated extracranial malformations are rare [Demeyer, 1967; Sedano et al., 1970]. However, the extracranial malformations that have been observed with FNM are seen with the most severe cases, type "D," and primarily involve limb anomalies [Sedano et al., 1970; Toriello et al., 1986].

While most cases of FNM occur as a sporadic and isolated finding, it has been observed as part of several genetically distinct syndromes, some with mendelian inheritance. These include Greig cephalopolysyndactyly syndrome, craniofrontonasal syndrome, and ophthalmofrontonasal dysplasia [Sedano and Gorlin, 1988]. In addition, the FNM phenotype has been associated with a partial duplication of chromosome 2:46XX,-7,+der(7),t(2;7)(q31;q36) [Chen et al., 1992].

The observation of genetic heterogeneity in FNM has led to the assertion that FNM is a nonspecific developmental field defect of the midline [Sedano and Gorlin, 1988]. A developmental field is a region of the embryo that reacts as a temporally and spatially coordinated unit to normal and abnormal developmental stimuli. Abnormal developmental stimuli, such as those caused by a teratogen or mutated gene, result in a developmental field defect. This is a localized group of primary malformations that originated from a single abnormality in development [Opitz, 1979, 1993].

Cloacal exstrophy is also thought to be a disorder of the midline developmental field. While it is often seen in association with a number of anomalies, it usually involves structures derived from the same developmental field. These include duplications of the vagina and uterus, underdevelopment of the colon with imperforate anus, malformed kidneys and ureters, and dysraphia of the lumbosacral spine, all of which are observed in this patient [Allen and Husmann, 1991]. Malformations in other regions of the body, such as craniofacial anomalies, are rare [Carey et al., 1978; Allen and Husmann, 1991].

In cloacal exstrophy, the primary pathologic event is the failure of the midline closure of the lower anterior abdominal wall. At around the 4th week of gestation, mesenchymal cells from the primitive streak migrate

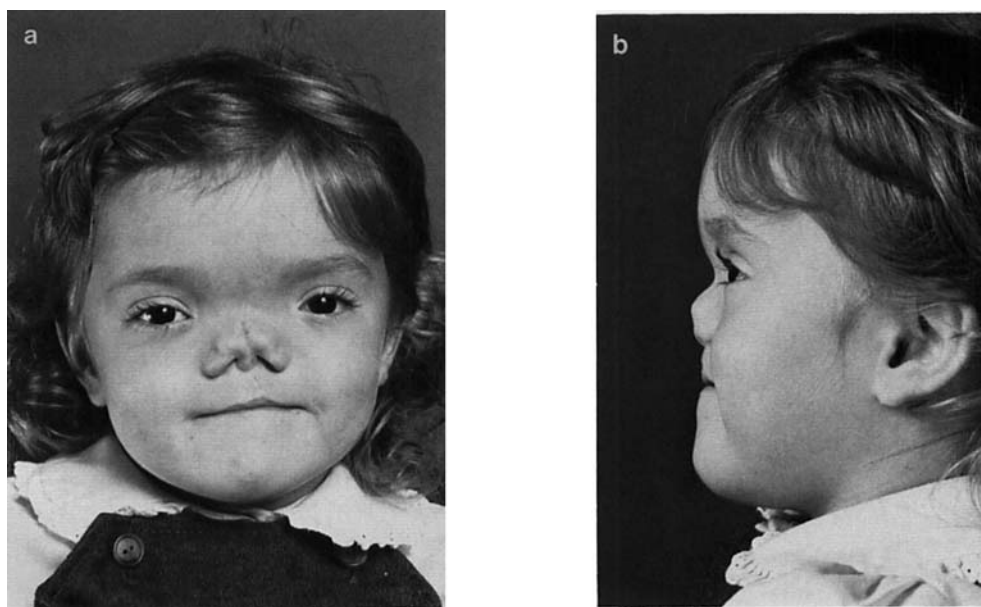


Fig. 2. The patient at age 6 years. **a:** Frontal view; **b:** profile.



Fig. 3. Sagittal MRI of the lumbosacral spine, showing the spinal dysraphia.

anteriorly to form the anterior abdominal wall. During this time, the cloaca is divided by the descending urogenital septum, with the anterior part becoming the bladder, and the posterior the hindgut. This septation is complete by the 6th week of gestation. Soon after, the cloacal membrane ruptures, opening the urinary and gastrointestinal tracts.

It is thought that in cloacal exstrophy, one pathologic mechanism is that the cloacal membrane is overdeveloped and provides a barrier to the normal migration of the mesenchymal cells. Thus, with rupture of the cloacal membrane prior to the completed urorectal septum, the lower abdominal structures eviscerate [Muecke, 1964]. If the cloacal septation is complete, the resulting malformation is the less severe bladder exstrophy [Gearhart and Jeffs, 1990].

Experimental models have supported this hypothesis. Muecke [1964] demonstrated in chicks that manipulation of the cloacal membrane produces cloacal exstrophy. However, in these animals, spinal anomalies were not observed. The explanation for the strong association of spinal dysraphia with cloacal exstrophy, as is seen in this patient, may be found in other animal studies [Cohen, 1991]. In hamsters, retinoic acid-induced excessive cell death in the primitive streak was found to cause both spinal dysraphia as well as abdominal wall defects [Shenefelt, 1972]. If this explanation is correct, it would suggest that there are two different paths to the formation of cloacal exstrophy, one involving abnormal cell death in the primitive streak, another due to a mechanical barrier (the overdeveloped cloacal membrane). This is consistent with the assertion that cloacal exstrophy is, like FNM, a field defect.

Experimental models have shown that both FNM and cloacal exstrophy can be caused by excessive cell

death, the former in the frontonasal prominence, the latter in the primitive streak. In each case, the key structures are affected at a similar time in gestation, at around 4 weeks gestation. One explanation for the occurrence of FNM and cloacal exstrophy would then be that this girl suffered some teratologic insult at approximately the 4th week of gestation, affecting the frontonasal prominence as well as the caudal primitive streak, causing excessive cell death in these regions. There was a known exposure to alcohol during this pregnancy. However, this would not seem to be a plausible explanation, as cloacal exstrophy is not associated with fetal alcohol exposure [Hannigan et al., 1992]. Similarly, FNM is not associated with fetal alcohol exposure, except for the single report of an infant with a FNM-like face that was thought to be due to prenatal exposure to both alcohol and cocaine [Robin and Zackai, 1994]. In addition, this young woman lacks the minor facial anomalies that suggest fetal alcohol syndrome [Clarren and Smith, 1978].

While no clear cause is apparent, it does seem evident that this patient's anomalies were the result of an abnormality of the developing caudal and cranial midlines during blastogenesis. Given the fact that these two anomalies arose at the same time in development, the lack of associated findings, and the normal psychomotor development, suggests that the findings in this girl represent an association, rather than a new syndrome [Lubinsky, 1986; Opitz, 1993]. As our understanding of what controls both normal and abnormal midline development evolves, it may then become clear what mechanism could have caused this constellation of findings.

## ACKNOWLEDGMENTS

N.H.R. was supported by NIH training grant 5T32HD07107.

## REFERENCES

- Allen TD, Husmann DA (1991): Cloacal anomalies and other urorectal septal defects in female patients: A spectrum of anatomical abnormalities. *J Urol* 145:1034-1039.
- Burk D, Sadler TW (1983): Morphogenesis of median facial clefts in mice treated with diazo-oxo-norleucine (DON). *Teratology* 27: 385-394.
- Carey JC, Greenbaum B, Hall BD (1978): The OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects). *BD:OAS X*(14):253-263.
- Chen H, Rightmire D, Zapata C, Fowler M, Hogan G, Wolfson J, Muenke M (1992): Frontonasal dysplasia and arhinencephaly resulting from unbalanced segregation of a maternal t(2;7)(q31;q36). *Dysmorph Clin Genet* 6:99-106.
- Clarren SK, Smith DW (1978): The fetal alcohol syndrome. *N Engl J Med* 298:1063-1067.
- Cohen AR (1991): The mermaid malformation: Cloacal exstrophy and occult spinal dysraphism. *Neurosurgery* 28:834-843.
- Cohen MM Jr, Sedano HO, Gorlin RJ, Kirasek JE (1971): Frontonasal dysplasia (median cleft face syndrome): Comments on etiology and pathogenesis. *BD:OAS 7*(7):117-119.
- Demeyer W (1967): The median cleft face syndrome. *Neurol Minneap* 17:961-970.
- Gearhart JP, Jeffs RD (1990): Exstrophy of the bladder, epispadias, and other bladder anomalies. In "Campbell's Urology," 6th Ed. Philadelphia: WB Saunders Co., pp. 1808-1811.
- Hannigan JH, Welch RA, Sokol RJ (1992): Recognition of fetal alcoholism and alcohol-related birth defects. In "Medical Diagnosis

- and Treatment of Alcoholism." Mendelson JH, Mello NK (eds.), pp. 639-667.
- Lubinsky M (1986): Current concepts: VATER and other associations: Historical perspectives and modern interpretations. *Am J Med Genet* [Suppl]2:9-16.
- Mueckke EC (1964): The role of the cloacal membrane in exstrophy: The first experimental study. *J Urol* 92:659.
- Opitz JM (1979): The developmental field concept in clinical genetics. *BD:OAS XV*(18):107-111.
- Opitz JM (1993): Blastogenesis and the "primary field" in human development. *BD:OAS XXIV*(1):3-37.
- Robin NH, Zackai EH (1994): Unusual craniofacial dysmorphism due to prenatal alcohol and cocaine exposure. *Teratology* 50:160-164.
- Sedano HO, Cohen MM Jr, Jirasek J, Gorlin RJ (1970): Frontonasal dysplasia. *J Pediatr* 76:906-913.
- Sedano HO, Gorlin RJ (1988): Frontonasal malformation as a field defect and in syndrome associations. *Oral Med Oral Pathol* 65: 704-710.
- Shenefelt RE (1972): Morphogenesis of malformations in hamsters caused by retinoic acid: Relationship to dose and stage of treatment. *Teratology* 5:103-118.
- Toriello HV (1986): Frontonasal "dysplasia," cerebral anomalies, and polydactyly. Report of a new syndrome and discussion from a developmental perspective. *Am J Med Genet Suppl* 2:89-96.